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REVIEW

Immune responses to zoster vaccines

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ABSTRACT

There are two licensed herpes zoster vaccines. One is a live vaccine (ZVL) based on an attenuated varicella-zoster virus (VZV). The other is a recombinant vaccine (RZV) based on the VZV glycoprotein E (gE) combined with AS01B, a multicomponent adjuvant system. RZV is superior to ZVL in efficacy, and differs from ZVL in that protection is not diminished by the age of the vaccinee and has not waned significantly during 4 years of follow-up. Immunologic studies demonstrated higher peak memory and persistence of T cell responses in RZV compared with ZVL recipients. RZV recipients also showed development and persistence of polyfunctional T cell responses. Taken together, we conclude that the immunologic data parallel and support the higher efficacy over time of RZV compared with ZVL.

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Pathogenesis of herpes zoster

Herpes zoster (HZ) has its origin during primary infection (varicella) with the varicella-zoster virus (VZV). VZV enters sensory and enteric neurons during varicella, either by retrograde movement in sensory nerves from skin and mucosal lesions or during the prolonged VZV viremia that is integral to varicella; or both.[1] Since most adults in the world (>95%) have developed varicella, they have the complete VZV genome latent in 5% of their neurons (~5–10 copies/latently infected neuron).[2,3] Latency is defined by the inability to recover the virus in tissue culture or visualize it by electron microscopy. A limited number of early transcripts and the viral proteins they encode have been previously detected in sensory neurons.[2] The details about latent gene replication are being re-evaluated, with some data suggesting that a single latency-associated transcript is the essential feature of VZV latency.[4]

Of equal importance for HZ pathogenesis is that varicella results in the appearance of VZV-specific humoral and T cell-mediated immunity (CMI). These are readily detected shortly before the rash and peak in the month after rash healing.[5] The VZV-CMI is essential for terminating varicella, and *also for preventing HZ* as described below.

Latent VZV reactivates intermittently to form infectious virions, as indicated by a variety of clinical and laboratory observations.[6-10] The frequency and magnitude of reactivation events are unknown, but the reactivations *typically remain subclinical because they are controlled by the VZV-specific immune responses that previously developed with varicella*. However, while post-varicella antibody responses remain relatively unchanged lifelong, VZV-CMI responses decline with age.[11] The correspondence of the age-related decline of these responses with the age-related increase in HZ frequency and severity, observed world-wide, is suggestive evidence for the essential role of VZV-CMI in preventing HZ.[12] Additional evidence includes the following observations: neither varicella nor HZ frequency and severity are increased in disease states defined solely by defects in antibody synthesis;[13,14] HZ frequency in immune compromised individuals correlates with VZV-CMI, but not with VZV antibody;[15] protection of immune compromised patients with an investigational VZV-based vaccine correlated with VZV-CMI and not antibody;[16] HZ continues to occur with high frequency after hematopoietic stem cell transplantation in spite of routinely providing passive immunization with γ-globulin products containing high titers of VZV antibodies;[17] the severity of HZ is prevented by pre-existing robust memory CMI, but not by high titers of VZV antibodies.[18]

These protective VZV-CMI responses wane with increasing age.[11] As a result, when latent VZV reactivates in sensory ganglia, and the local immune responses have become *inadequate to prevent propagation of the infection*, VZV infection will spread within the ganglia (which often causes neuropathic pain) and will spread antegrade to the skin to cause the characteristic painful HZ rash (called nociceptive pain) in the dermatome innervated by that ganglion. It then follows that *the goal of a successful HZ vaccine is to restore VZV-specific CMI responses that decline during the aging process* (or as a result of iatrogenic or disease-related immune compromise).

Live attenuated HZ vaccine (ZVL)

Clinical

The first licensed HZ vaccine consisted of the attenuated Oka (Merck) strain of VZV that also comprises the varicella vaccine. The dose administered was 14-fold greater than is used to prevent

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varicella. The utility of this HZ vaccine was determined in participants 50 to >80 years old and was characteristic of many vaccines for older people, namely its efficacy was progressively lower as the age of the vaccinee increased (70% in age 50–59; 64% in age 60–69; 38% age 70–79; 18% age >80 years)[19-21] (Table 1). However, vaccine efficacy was greater against severity (67% average) of HZ and this protection against severe pain did not vary as much with age. ZVL efficacy against HZ waned significantly at 5–8 years after vaccination, but it had better persistence against severity of HZ.[22] Nevertheless, ZVL was an important advance that annually prevented >100,000 severe cases of HZ during recent years. Effectiveness studies suggested that the age effect on efficacy was less and the persistence of efficacy against post-herpetic neuralgia was preserved longer than in the placebo-controlled pivotal trial.[23,24] ZVL was safe, well tolerated, and required a single dose. However, it was contraindicated for immune compromised patients, who make up about 10% of HZ cases annually in the US.[25]

Immunologic

In a substudy of the pivotal ZVL trial, we showed that VZV-specific antibody and two measures of T cell immunity (CMI) were stimulated by the vaccine.[26] The kinetics of the immune responses were similar to those of efficacy of the vaccine – immunogenicity was greater in the first 6 months after administration and waned significantly within 3 years. Furthermore, the extent of the immune enhancement from vaccination was inversely related to the age of the vaccinee. This substudy also indicated that protection from HZ correlated with the magnitude of the VZV-specific immune responses that were present at the time of vaccination; at 6 weeks after vaccination; and in the last measurement available prior to the diagnosis of HZ. This was most evident with VZV-specific CMI, but was also observed with antibody responses. The additional large clinical trial of people 50–59 years of age showed that the 6-week antibody response was a correlate of protection.[20]

Subsequent studies showed that ZVL not only increased the magnitude, but also the breadth and polyfunctionality of VZV-specific CD4+ and CD8+ T cell responses.[26-29] Epitopes recognized by CD8+ T cells that were increased by vaccination predominantly concentrated on ORF9 immediate early gene products, whereas CD4+ T cell responses targeted epitopes on multiple gene products including IE63, IE62, gB, ORF9 and gE in hierarchical order.[27,28] New CD4+ and CD8+ T cell responses were at least partially maintained for up to 6 months[27].

To identify the defects that might account for reduced efficacy as a function of increasing age, we compared T cell responses to ZVL in young and older adults and found both phenotypic and functional differences. Older adults displayed robust increases in VZV-specific senescent CD8+ CD57+ T cells after vaccination and lower numbers of polyfunctional CD4+ and CD8+ Th1 responses (IL2, IFNg and CD107a markers) compared with young adults.[30] Our findings were in accordance with another study showing that older vaccinees lost T cell responses acquired after vaccination more rapidly than younger vaccinees.[31] The T cell attrition was associated with a specific gene expression signature in cell cycle, cell division, DNA repair and mismatch repair modules. Additional transcriptomic and metabolomic signatures also differentiated young and older adults after vaccination, but these correlated best with peak antibody responses to ZVL.[32] We and others also showed that older adults with high proportions of regulatory T cells had low Th1 responses to ZVL.[33,34] Collectively, these studies show that immunologic changes characteristic of immune senescence profoundly affect T cell responses to ZVL.

Given the age effect on immunity induced by ZVL and waning of the initial response over time, attempts were made to enhance or restore VZV-specific immunity. Intradermal administration was dose-sparing (3-fold less required vs subcutaneous administration) and was more effective in stimulating VZV-specific CD4+ central and effector memory responses.[35] A strategy to restore waning VZV-specific immunity utilized a second dose of ZVL, administered 10 years after an initial dose.[36] This resulted in a significant increase in VZV-CMI measured 1 year later, achieving levels higher than those of age-matched controls immunized for the first time. However, at 3 years the boosted group maintained only a marginal advantage in IFNγ+IL2+ effector memory T cells over the first-time immunized individuals.[37]

Recombinant glycoprotein E (gE) adjuvanted HZ vaccine (RZV)

This vaccine is based on a single VZV glycoprotein which is abundantly expressed by VZV-infected cells and is the largest component in the viral envelope.[38] gE is also a major target of antibodies and CD4+ T cell responses to VZV. This antigen is combined with an adjuvant system (AS01B) that contains 3-O-desacyl-4-monophosphoryl lipid A (MPL) and a triterpene plant product (Quillaja saponaria Molina, fraction 21 [QS21]). The adjuvant components are packaged in liposomes.

Table 1. Comparison of herpes zoster vaccines licensed in the US.

Characteristic	Zoster Vaccine Live	Recombinant Zoster Vaccine
Antigen	Live attenuated VZV (vOka)	Recombinant viral glycoprotein (gE)
Doses Delivered	~36 million	>3 million
Adjuvant	None	AS01B
Overall Efficacy	51%	91%
Age Effect	Pronounced	Minimal
Reactogenicity	Low	High
Persistence of protection	5 to 8 years	≥4 years*
Doses	One	Two (separated by 2 to 6 months)
Protection with 1 dose	Yes	Limited – need 2 doses

* Studies done up to 4 years.

Clinical

Two placebo-controlled trials were completed, including >30,000 participants ≥50 years old, among which 16,500 were ≥70 years old. The trials documented an efficacy unique for older vaccinees, of 97% overall and 91% for those ≥70 and ≥80 years old[39,40] (Table 1). This protection persisted at 85–89% for at least 4 years after vaccination in participants >70 years old. Follow-up is proceeding for an additional 6 years, although there will be no placebo comparator group. The strong adjuvant contained in RZV is associated with significant reactogenicity. Grade III (limits normal daily activity) injection site reactions occurred in 8.5% of vaccinees vs 0.2% of placebo recipients. Grade III systemic reactions occurred in 6–11% of vaccinees vs ~2% of placebo recipients. Older individuals were less likely to have grade III reactions; severity of reactions did not differ appreciably between the two doses. There was no safety signal for serious adverse events or possible immune mediated diseases. A trial in autologous hematopoietic stem cell transplant recipients demonstrated 68% efficacy against HZ and 89% efficacy against PHN.[41]

Immunologic

The remarkable protection offered to individuals of advanced age is largely due to the adjuvant system. Pre-clinical studies (using gE and hepatitis B antigens) and Phase I and II studies established that optimal immune responses, both antibody and CMI, required that all components of the adjuvant system and gE be co-localized without any significant interval between administration of the components.[42-44] A synergistic effect was demonstrated between MPL and QS21, and two doses of RZV were required for optimal responses. The absence of an age effect on response to RZV was apparent from these early experiments.

The subsequent two pivotal clinical trials included an immunology substudy. This showed that gE antibody titers, measured by ELISA at one month after the second dose of RZV, increased in 98% of vaccinees.[45] The mean increment in antibody titer was 39-fold, persisting as 8.3-fold higher than baseline at 3 years after vaccination. The decline in antibody titers was slightly greater in the oldest individuals. VZV-specific CMI was measured by flow cytometry to detect Th1 biomarker expression after ex vivo stimulation with gE overlapping peptide pools. Responses defined by CD4+ T cells expressing 2 or more markers among CD40L, IFNg, TNFa and IL-2 occurred in 93% of vaccinees. These declined to 57% at 3 years, with levels lower at all time points in people > 79 years old. The mean increase in VZV-CMI, which was 25-fold shortly after vaccination, fell to 7.9-fold at 3 years. As the interval after vaccination increased, the proportion of polyfunctional cells increased, such that at least 50% of VZV-specific CD4+ T cells had 3 or 4 biomarkers at 3 years after immunization. This was similar for all age groups vaccinated. Since 43% of vaccinees lost the RZV-induced CMI boost at 3 years after immunization, while they remained protected against HZ, this suggests that the measures of immunity in these trials were likely not correlates of protection.

The substudy confirmed the importance of the second dose of vaccine, which was administered 60 days after the first. A small clinical trial indicated that a 6 month interval between doses resulted in non-inferior immune responses. The kinetics of gE-specific immune responses were determined at 6 and 9 years after vaccination.[46,47] Antibodies declined for 2 years and plateaued subsequently; CMI declined for 4 years before stabilizing. Both types of responses remained above pre-vaccination levels and there was little age effect observed. Because the substudy had a limited sample size (2900 for antibody assessment; 430 for CMI) and because of the paucity of HZ cases in the RZV recipients, it was not possible to define an immune surrogate of protection.

Immune compromised patients are an important target population for RZV. In addition to the efficacy mentioned above for autologous stem cell recipients, RZV induced gE antibodies in 67–72% and gE-specific CMI in 50–80% of patients with hematologic and solid malignancies receiving chemotherapy, and of renal transplant recipients. Immunogenicity was limited in allogeneic transplant recipients and in any vaccinees who received RZV during courses of chemotherapy.[48-50]

To understand the basis for the different immunogenicity and efficacy of the two zoster vaccines, we compared immune responses to the ZVL and RZV in adults 50 to 85 years old.[51] gE-specific T cells were very low or undetectable before vaccination when analyzed by FluoroSpot and flow cytometry. Both ZVL and RZV increased gE-specific responses, but at 30 days after the last dose of each vaccine, corresponding to the peak memory response to vaccination, gE-specific CD4+ and CD8+ effector and memory T-cell responses were ≥10-fold higher in RZV compared with ZVL recipients. In addition, VZV-specific T cell memory responses were higher in RZV recipients, whereas CD8+ cytotoxic and effector T cell responses were higher in ZVL recipients. VZV- and gE-specific regulatory T cells expressing FOXP3 or immunologic checkpoints were also increased in RZV compared with ZVL recipients. At 1 year after vaccination, all gE-Th1 and VZV-memory responses remained higher in RZV compared to ZVL recipients. Mediation analyses showed that peak memory responses to gE or VZV were necessary for the persistence of Th1 responses to either vaccine. For example, the VZV-specific peak memory response in RZV recipients explained 73% of the total effect of RZV on persistence of its immunogenicity. Among effector responses, polyfunctional responses including IFNg, IL2 and TNFa were more common among RZV compared with ZVL recipients. The difference in the responses to RZV and ZVL is somewhat reminiscent of the difference between immune responses in older adults and young adults, with respect to memory, persistence and polyfunctionality, suggesting that RZV is able to neutralize the effects of immune senescence that are quite prominent on the responses to ZVL.

Studies of the AS01B Adjuvant System in several non-primate animal models showed that this adjuvant enhanced immune responses by increasing the number of activated antigen presenting cells (APC).[52-54] While these studies did not utilize gE antigen, they are likely informative for understanding the RZV results, and some conclusions were confirmed with gE in non-human primates. Shortly after immunization the local innate response resulted in an influx to the draining lymph node (dLN) of conventional dendritic cells (cDC), as well as neutrophils and monocytes that carried

most of the gE antigen. Likely, because of QS21 transported from the injection site, subcapsular sinus macrophages produced IL12 and IL18, which signaled resident NK and CD8+ unconventional virtual memory T cells to produce large amount of IFNg. This also activated CD11c+ cDC. Within 24 hours after vaccination there was a 200-fold increase in monocytes in the dLN and an 8.6-fold increase in cDC. A correlate in the blood compartment of these events in the dLN was an increase of IFNg and circulating polyfunctional CD4+ T cells.

Gene transcription profiling of the dLN indicated enrichment of cytokine transcription pathways, especially those involved in interferon-signaling, within 4–6 hours of vaccination. Numerous genes were transcriptionally active, including emergent genes that were represented only when both components of the adjuvant system were present. This confirmed the synergistic interaction of both components of AS01B.

Inactivated (non-live) zoster vaccine (ZVI)

Since ZVL, a live VZV vaccine, was contraindicated for immune compromised people, development of a non-live vaccine was undertaken before RZV was in clinical trials. ZVI was prepared by inactivation (heat or irradiation) of the attenuated VZV (Oka/Merck) used in the varicella vaccine and ZVL. Efficacy was demonstrated in autologous hematopoietic stem cell transplant recipients utilizing a dose prior to transplantation and 3 additional monthly doses after transplantation. At one year after vaccination 7/53 (13%) of vaccinees developed HZ versus 19/58 (33%) of placebo-recipients. Protection correlated with VZV-CMI, but not antibody.[16,55] ZVI was not immunogenic in allogeneic stem cell transplant recipients.[56,57] A phase III trial in autologous stem cell transplant recipients using the 4-dose schedule and γ-irradiated VZV, demonstrated an efficacy against HZ of 64%; against complications of HZ of 74%; and against PHN of 84%[58] at a mean 2.3 year follow-up. In our opinion, because of the success of RZV, this potential competitor is unlikely to be further investigated.

Concluding remarks

The striking efficacy of RZV has brightened the horizon for vaccines for elderly individuals. RZV demonstrates that a single viral glycoprotein can stimulate robust and lasting protective responses, providing that an appropriate adjuvant shapes that response. That AS01B was able to overcome the limitations resulting from immune senescence suggests that appropriate adjuvantation might improve other vaccines needed for this population. It is important to note that although RZV is more reactogenic than other vaccines, especially with respect to systemic adverse events, over 3 million people have successfully taken both doses of the vaccine to date. Nevertheless, equally effective vaccines with less side effects, which could also be administered as a single dose are desirable.

Current and proposed studies of RZV should provide mechanistic insight that will be useful in designing future vaccines. The knowledge that can be gathered from peripheral blood studies is limited. Rather, a better understanding of the mechanism of action of RZV may be obtained from studying human draining lymph nodes and other tissues, as suggested by the animal models.

This new vaccine is likely to fill the unmet need of protecting immune compromised individuals from HZ. Many clinical trials to demonstrate safety and efficacy in such patients are in progress. These trials may also provide an immunologic correlate of protection. At least four studies of RZV in immune compromised individuals have been undertaken (renal transplant, hematologic malignancies, solid tumor with chemotherapy and autologous hematopoietic stem cell transplant). HZ break through will likely be more common in these immune compromised populations and, in conjunction with the immunologic studies performed in these trials, it may be possible to identify an immunologic correlate of protection.

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